



ThalassemiaNEWS

A quarterly newsletter keeping the medical and patient community in touch with thalassemia developments

Autumn 2022

IN PROFILE

An in-depth view of an organization or individual involved in thalassemia

In this Issue, we bring you excerpts from an interview with β -thalassemia patient NinaMaria Badalamenti, a 26 year old news producer living in Indianapolis, United States.

'Growing up with thalassemia involved a lot of hospital visits, a lot of tests, surgery and regular transfusions. I've been blessed with a really good care team that I've had pretty much my whole life. I missed some school and that was kind of hard – kids started to notice. So it was a little bit of a struggle for a while. But my parents instilled in me that thalassemia wasn't going to hold me back. And that you go on and live a normal life, just have the mindset that I can be normal, I can do anything. I just need to do what the doctor recommends, and take care of my health.'

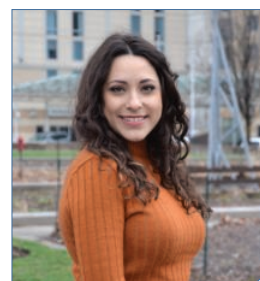
'I've been **transfusion dependent** my whole life. Most of my childhood, it was every three weeks that I got a transfusion. Now I'm up to every four weeks, but that's kind of my max. We've learned a good

balance and what I need to get through those four weeks.'

'It's been **challenging** figuring out when and how to explain thalassemia to others. Especially growing up, kind of keeping it to myself. It's been a little bit scary. But what I've learned is to just let it happen naturally and not to be ashamed. Most of the time people are intrigued, they're interested. It's something that I'm finally able to do comfortably.'

'I've learned that I'm a lot stronger and more capable than I ever thought I was. I've allowed thalassemia to be something that gives me strength.'

'I'd advise anyone new to thalassemia not to be ashamed – everyone has something and this is your thing. Most people are a



NinaMaria Badalamenti

lot more accepting than you think they're going to be. Secondly, take your health in your own hands. So find a good care team, find a good doctor and listen to them. And also, know your own health, you know your body more than anyone else. So you need to listen to it and work with your doctor to live your fullest life and not allow it to bring you down.'

The full interview can be viewed here. 

Compensation was provided to this patient for the time required for this interview

IN-DEPTH : THE GLOBAL EPIDEMIOLOGY OF THALASSEMIA

Providing an in-depth analysis of recent publications

Thalassemia is a rare disease, and so global prevalence of the thalassemias, and α -thalassemia in particular, have not been well characterized¹. Despite the data scarcity, it is becoming clear that the global epidemiology of thalassemia is changing.

Thalassemia has historically been associated with areas of the Mediterranean and Southeastern Asia that had widespread malaria. Thalassemia provides protection against malaria, giving rise to genetic selection for the thalassemia mutations in regions where malaria is endemic. Population screening, improved survival rates, and migration, however, have led to a shift in the prevalence and geographical spread of thalassemia²⁻⁵. Improvements in screening and management approaches have enabled more affected individuals to reach adulthood. The ease with which people can relocate across large distances in recent years has facilitated the dispersion of thalassemia carriers far from the areas traditionally associated with a high prevalence. Consequently, thalassemia is becoming more common in areas previously not known for the disease, such as Northern Europe and North America.



Understanding of the global prevalence of thalassemia is limited, with population-based prevalence estimates being unavailable for many countries and outdated for others. The Thalassemia International Federation has taken action to remedy this, developing a platform for a global thalassemia registry, and is calling for worldwide collaboration to adopt a standardized reporting of thalassemia cases⁶. A global registry would also provide valuable information on disease burden and management and highlight challenges to the care of thalassemia so action can be taken to address them.

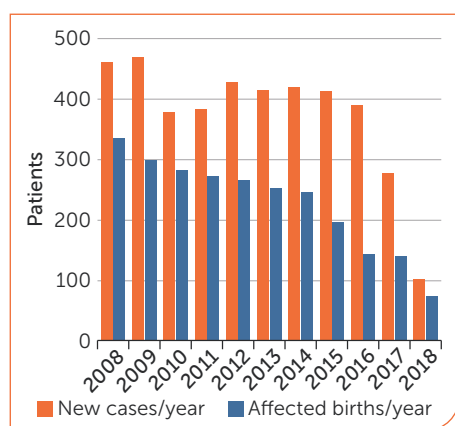
Some of the most recent population-based data are summarized here.

Asia

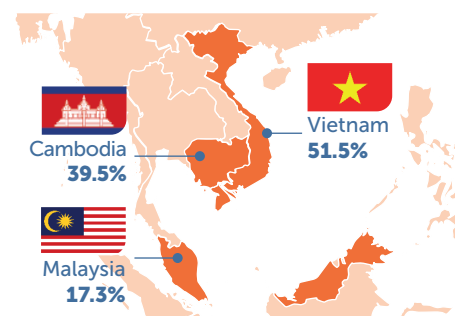
Thalassemia has historically been highly prevalent in Southeast Asia, where up to 40% of the population are suspected to be genetic carriers.

In 2018, the Malaysian Thalassemia Registry included 7984 patients living with clinically significant forms of thalassemia⁷. The majority of cases were in the east of the country where there is a high indigenous population. The most common diagnosis, affecting just over a third of patients (34.37%) was hemoglobin E/ β -thalassemia, closely followed by β -thalassemia major (33.52%). Alpha-thalassemia was grouped with other less common thalassemias, which together accounted for less than 5% of cases. Analysis of Registry data highlighted the decline in the prevalence of thalassemia in Malaysia over the last decade. There were only 74 affected births in 2018 compared with 334 in 2008 (Figure 1)⁷.

Figure 1. Prevalence of thalassemia in Malaysia 2008-2018⁷



The carrier rate of α -thalassemia in South-eastern Asia was recently reported to be 22.6%, but it should be noted that the systematic review from which this figure was calculated included some non-population based analyses⁸. Of the Asian countries studied, Malaysia had the lowest rate (17.3%) compared with 51.5% in Vietnam and 39.5% in Cambodia. Geo-population modelling for Thailand as part of a large Southeast Asia project suggests that the prevalence of α -thalassemia may be greater than historically thought⁹.



Thalassemia has not historically been present in Northeastern Asia, but cases in this region are becoming more common. Analysis of the Korean National Health Insurance database published in 2022 revealed an increase in the prevalence of thalassemia from 0.74/100,000 in 2006 to 2.76/100,000 in 2018. Much of the increase occurred

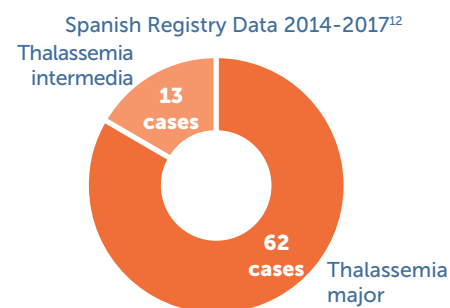
between 2016 and 2018 when the incidence rate almost doubled (0.22/100,000 in 2016; 0.41/100,000 in 2018). Prevalence of thalassemia increased with increasing age within the Korean population, reflecting the effectiveness of early management strategies in extending survival¹⁰.

Europe

Until recently, thalassemia in Europe was only considered likely within populations of the Southernmost regions of Italy and Greece. Indeed, Greece has been historically associated with a relatively high prevalence. Analysis of The National Registry for Hemoglobinopathies in Greece from 2010-2015 (N=4032) reported 213 cases of α -thalassemia and 2759 cases of β -thalassemia. However, compared to the previous analysis of the database, there had been a reduction in both the total number of hemoglobinopathy diagnoses and the number of affected births¹¹.

In contrast, the prevalence of thalassemia in other Mediterranean countries not traditionally associated with thalassemia appear to have increased. Analysis of data held in the Spanish Registry of Hemoglobinopathies for 2014-2017 identified 75 cases of thalassemia, 62 of which were thalassemia major, and 13 cases of thalassemia intermedia¹². These reported cases likely underestimate country-wide prevalence, as the registry only recently extended its remit from a pediatric registry to begin enrolling adults.

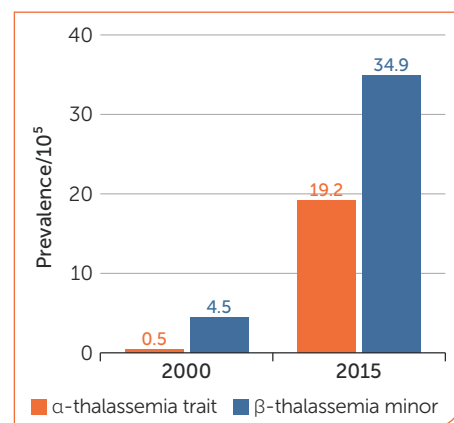
These limitations highlight the need for further epidemiology studies to better understand the prevalence in Spain.



Cases of thalassemia are now also being reported in Northern Europe. A retrospective cohort analysis of data from National Health Service (NHS) in England for 2009-2018 identified 612 cases of transfusion-dependent β -thalassaemia¹³. More recently, The National Haemoglobinopathy Registry for England 2019/2020 recorded 1744 cases of thalassemia¹⁴. The vast majority of cases were β -thalassemia major.

Similarly, analysis of data from the Danish National Patient Register and laboratory database of red blood cell disorders revealed an increase in the prevalence of hemoglobinopathies. The prevalence of α -thalassemia trait in Denmark increased 41-fold from 2000 to 2015 and β -thalassemia minor increased eight-fold¹⁵.

Figure 2. Shift in prevalence of thalassemia in Denmark¹⁵



North America

Current estimates of the prevalence of thalassemia in North America are limited. Retrospective analysis of thalassemia treatment in the US using 2016 data from the MarketScan Commercial and Medicaid Multi-State Database identified 8,480 patients with a diagnosis of β -thalassemia¹⁶. As of 2015 California was the only state to have mandatory standardized reporting for α - and β -thalassemia disorders. At that time, almost 14,000 individuals in California were reported to have a thalassemia diagnosis and the majority were Asian¹⁷.

Take home messages

- Thalassemia is becoming an increasingly global disease due to migration patterns
 - Prevalence no longer correlates with endemic malaria
 - Prevalence remains high in Southeast Asia and the Mediterranean but is increasing in Northern Europe and North America
- Few data are available for the prevalence of α -thalassemia
- Current prevalence data from population studies are not available for β -thalassemia in many countries, including the US
- Standardizing thalassemia reporting in a global registry will help to better clarify the global epidemiology

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PATIENT COMMUNITY RESOURCES

Discover new resources for the thalassemia patient community and their caregivers



Sharing experiences of living with thalassemia, practical lifestyle tips, and the latest research findings can provide invaluable support and reassurance between clinic visits. The thalassemia podcast—Thal Pals: The Alpha Beta Revolution™ which has recently launched, enables ongoing collaboration between pa-

tients, caregivers, and medical experts. The monthly broadcasts feature members of the thalassemia community from around the world discussing current topics relevant to both α - and β -thalassemia. It provides a forum for patients with thalassemia, or their caregivers, to tell their stories, and for experts in the field to explain different aspects of the disease, various management approaches, and the practical impact of recent advances in thalassemia.

You can access the first podcast here



Coming soon

Fast Facts – A series of educational booklets written by experts, covering those key topics patients, families and caregivers are most interested in.



CLINICAL TRIALS UPDATE

Sharing the latest news on clinical trials in thalassemia

Mitapivat (AG-348) is an oral, small-molecule allosteric activator of red blood cell (RBC) pyruvate kinase (PK) that increases RBC energy metabolism through elevated adenosine triphosphate (ATP) production, which in turn may lead to improvements in RBC maturation, survival, and function. It is in clinical development across a range of hemolytic anemias, including both α -thalassemia and β -thalassemia.

Data from a proof-of-concept phase II trial in non-transfusion-dependent α - or β -thalassemia (NTDT) showed an increase in hemoglobin level (Hb) from baseline in 80.0% (16/20) of patients between Weeks 4 and 12.¹ The average increase in Hb from baseline was 1.3 g/dL.¹

Phase III studies evaluating the efficacy and safety of mitapivat in patients with α - or β -thalassemia are now underway ([NCT04770753](https://www.clinicaltrials.gov/ct2/show/study?term=NCT04770753&rank=1), [NCT04770779](https://www.clinicaltrials.gov/ct2/show/study?term=NCT04770779&rank=1)).

More information can be found at <https://www.energizeclinicaltrials.com/hcp/energize-t> (website for healthcare professionals) and <https://www.energizeclinicaltrials.com/> (website for patients).

Phase III ENERGIZE trial (NCT04770753; 2021-000211-23)



Design

ENERGIZE is a phase III, randomized, double-blind trial evaluating the efficacy and safety of mitapivat relative to placebo in patients with NTDT.² Eligible patients will have α - or β -thalassemia, have received ≤ 5 RBC units during the previous 24 weeks and not needed RBC transfusions for ≤ 8 weeks, be aged ≥ 18 years, and have Hb ≤ 10.0 g/dL (estimated N=171).

Mitapivat 100 mg or matching placebo (2:1 randomization) will be administered twice daily for 24 weeks. Patients completing the 24-week study period can continue in the open-label extension to receive mitapivat for up to an additional 5 years.

The primary endpoint of the ENERGIZE trial is the proportion of patients in whom Hb increases by ≥ 1.0 g/dL from baseline between Week 12 and Week 24. Secondary

endpoints include change from baseline in mean Hb, change from baseline in mean fatigue subscale score of the Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue) scale from Week 12 to Week 24, and markers of hemolysis and erythropoiesis.

Latest trial status

As of 9/14, this global trial has 38 study sites open and is estimated to complete in December 2023.

Phase III ENERGIZE-T trial (NCT04770779; 2021-000212-34)



Design

ENERGIZE-T is a phase III, randomized, double-blind trial evaluating the impact of mitapivat on transfusion burden compared with placebo in patients (estimated N=240) with transfusion-dependent thalassemia (TDT).³ Eligible patients will be ≥ 18 years old and have α - or β -thalassemia requiring

transfusion of 6 to 20 RBC units and a ≤ 6 -week transfusion-free period during the 24 weeks prior to enrolling

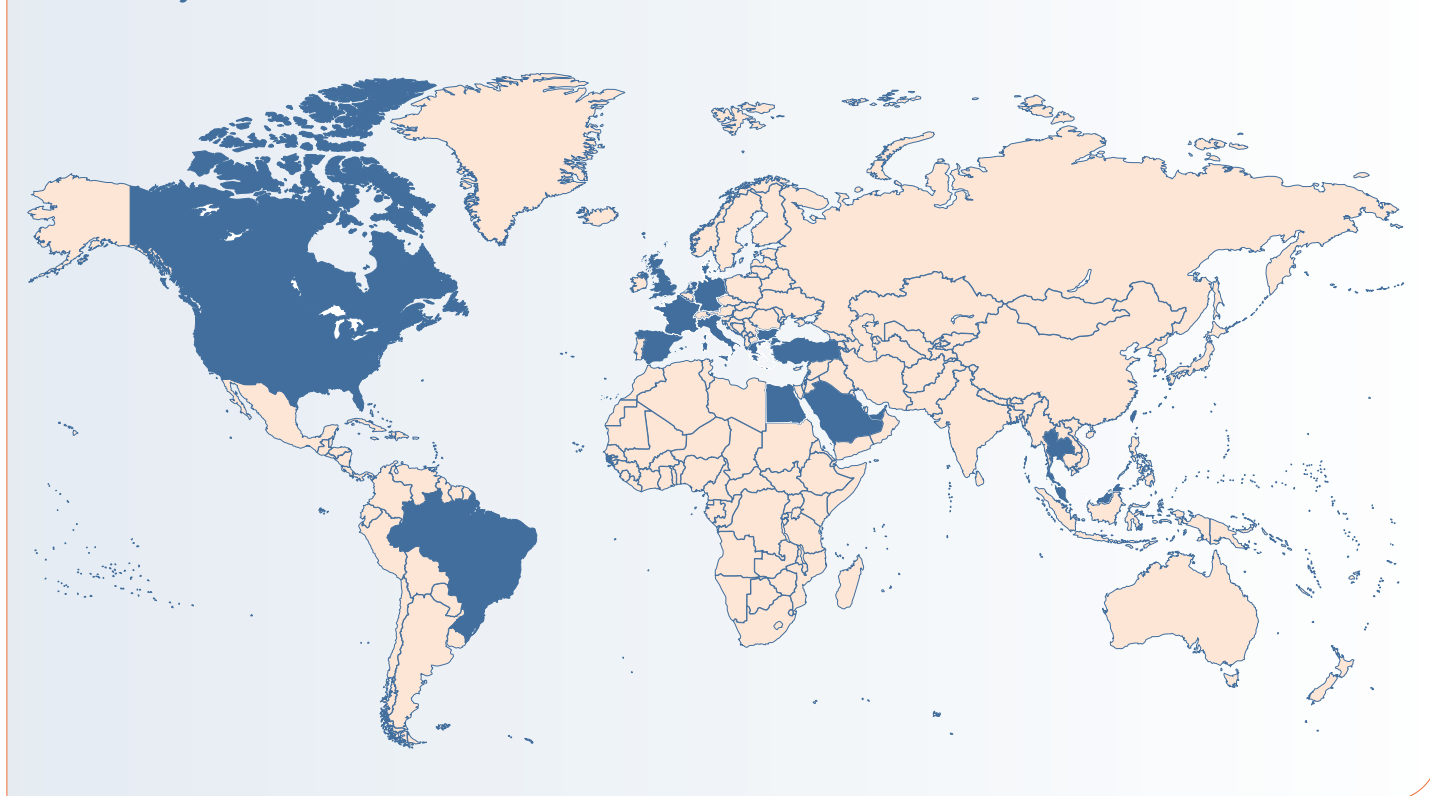
Mitapivat 100 mg or matching placebo (2:1 randomization) will be administered twice daily for 48 weeks. Patients completing the 48-week double-blind intervention phase can continue in the open-label extension phase to receive mitapivat for up to an additional 5 years.

The primary endpoint of the ENERGIZE-T trial is the proportion of patients who achieved a $\geq 50\%$ reduction in transfused RBC units during any consecutive 12-week period. Secondary endpoints include the proportion of patients with $\geq 50\%$ reduction from baseline in transfused RBC units during any consecutive 24-week period and change from baseline in number of RBC units transfused from Week 13 to Week 48.

Latest trial status

As of 9/14, this trial has 42 study sites open for recruitment and is estimated to complete in June 2024.

Planned study sites for ENERGIZE and ENERGIZE-T



References

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2. A Study Evaluating the Efficacy and Safety of Mitapivat in Participants with Non-Transfusion-Dependent Alpha- or Beta-Thalassemia (α - or β -NTDT) (ENERGIZE). ClinicalTrials.gov Identifier: NCT04770753.
3. A Study Evaluating the Efficacy and Safety of Mitapivat in Participants with Transfusion-Dependent Alpha- or Beta-Thalassemia (α - or β -TDT) (ENERGIZE-T). ClinicalTrials.gov Identifier: NCT04770779.

KEY DATES

October 17-20, 2022

Eleventh Cooley's Anemia Symposium, New York, NY, USA

October 20-22, 2022

17th Annual Sickle Cell and Thalassemia Conference (ASCAT), London, UK

December 10-13, 2022

64th ASH Annual Meeting, New Orleans, LA, USA

April 27-29, 2023

International Summit on Hematology and Blood disorders | Orlando, FL, USA

May 8, 2023 12:00 AM - May 9, 2023 12:00 AM

World Thalassemia Day

June 8-11, 2023

European Hematology Association (EHA) Congress, Hybrid and Frankfurt, Germany

EDITORIAL POLICIES & TEAM

The objective of this newsletter is to provide updates on new scientific information, resources, and activities of interest to the thalassemia medical and patient community. The newsletter content is prepared by thalassemia experts in collaboration with Agios Pharmaceuticals. All of these experts serve as paid consultants for Agios Pharmaceuticals.

The following experts are involved in this initiative

- Khaled Musallam, MD, PhD
- Sujit Sheth, MD
- Thomas Coates, MD
- Vip Viprakasit, MD, DPhil
- Ali Taher, MD, PhD
- Hanny Al-Samkari, MD
- Kevin Kuo, MD
- Maria Dominica Cappellini, MD

Mitapivat is not approved for the treatment of thalassemia by any health authority. The safety and efficacy of mitapivat in thalassemia are under investigation and have not been established. There is no guarantee that mitapivat will receive health authority approvals or become commercially available in any country for the uses under investigation.

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